wherein $Z[D]_y$ is capable of crossing the membrane of the and is capable of being hydrolyzed therein to release D.

REMARKS

Reconsideration of the present application, as amended, is respectfully requested.

Please replace pending claims 1, 2, 6-9, 12, 13, 31-33 with the revised form of the claims and add new claims 35-37. Attached hereto is a marked-up version of the changes made to the specification and claims by the amendment. The attached appendix is captioned **"Version with Markings to Show Changes Made."**

Applicants wish to thank the Examiner for the courtesies extended during the interview conducted on February 25, 2003. Applicants have amended the claims in accordance with the proposal faxed to the Examiner in advance of the interview and as further modified during the interview.

A. STATUS OF THE CLAIMS

As a result of the present amendment, claims 1-16 and 18-37 are presented in the case for continued prosecution. It is urged that all of the informalities and claim objections made by the Examiner in the office action have been addressed by the present amendment. It is further urged that the claims and specification are in proper form in all respects and that no new matter has been added. New claim 35 provides the plural of the singular terms where appropriate in claim 17, now cancelled. New claims 36 and 37 are independent claims based on the combination of claims 1 and 9 (for claim 36) and claims 1 and 14 (for claim 37).

B. INFORMALITIES, CLAIM OBJECTIONS AND 35 USC SECTION 112 REJECTIONS

On pages 2-3 of the office action, the examiner has noted informalities in the claims and specification. It respectfully submitted that the application is now in proper form and that all of the informalities have been attended to.

C. OBVIOUSNESS DOUBLE PATENTING REJECTION HAS BEEN MOOTED

Claim 8 has been amended to delete the possibility of D being H. As discussed during the interview, it is believed that this amendment renders the rejection moot. Reconsideration and removal of the rejection in view of U.S. Patent No. 6,180,095 is therefore requested.

D. CLAIM 8 IS PATENTABLE OVER THE CITED ART

The Examiner has rejected the subject matter of claim 8 under 35 USC Section 102(e) in view of U.S. Patent No. 6,180,095 and under 35 USC 102 Section (b)in view of Greenwald et al. It is urged that the amendment of claim 8 to eliminate H from the claim renders the claim patentable over each of the cited references. Reconsideration and removal of the references is therefore requested.

E. THE AMENDED CLAIMS ARE PATENTABLE OVER ZIER

In paragraph 12 of the office action, the Examiner has taken the position that the subject matter of claims 1, 2, 4-6, 8, 13, 16-18, 20, 21, 23, 24 and 27 is anticipated by Zier et al. The Examiner further pointed out in the interview summary that amendment of claim 1 to include further description of $[D]_y$ in accordance with the language found on page 8, line 31 of the specification would allow the claims to distinguish over the reference. In response, Applicants have amended the claim to recite that that $Z[D]_y$ is capable of crossing the membrane of the and is capable of being hydrolyzed therein to release D. As was pointed out in the interview, Z must release D and Zier does not teach such a compound. It is respectfully submitted that the peptide of Zier would not break down in the way required by the amended claims. For example, it is believed that if the rejection were to be maintained, it would have to be true that when Z is Glu, it must release the rest of the peptide after the polymer-hydrolyzes. It probably must also release the terminal Ala in view the necessity to liberate the D moiety. The original peptide is no where to found for release in the cell as is the case with the present invention. At best, it is speculated that Zier et al. if administered, releases a shorter peptide which does not

include Z. Zier thus does not disclose a polymeric composition which is designed to allow the release of the originally attached material. There is no disclosure or suggestion of how to achieve such a result in Zier. Reconsideration and removal of the rejection is therefore requested.

The Examiner has also rejected the subject matter of claims 25 and 26 as being obvious over Zier et al. It is respectfully submitted that these dependent claims distinguish over Zier by virtue of the amendment discussed above and their dependency on claim 1. Removal of the rejection is therefore requested.

F. INDICATION OF ALLOWABLE SUBJECT MATTER

The Examiner has indicated that several of the dependent claims would be allowable if the informalities were addressed and if they were made to include all of the limitations of the base claims. Applicants note the indication of allowable subject matter with appreciation but urge that in view of the amendments made herein, all of the claims are allowable as currently presented.

G. FEES

This response is being filed with a Petition for a One Month Extension of Time. No further fees are believed to be required. If, on the other hand, it is determined that any further fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to deposit account number 50-0217.

Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 50-0217.

H. CONCLUSION

In view of the actions taken and arguments presented, it is respectfully submitted that the present application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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Docket No.: 213.1079-CIP3

UNITED STATES PATENT & TRADEMARK OFFICE

Examiner: RUSSEL, J.E. Art Unit: 1654

Re: Application of: GREENWALD, R.B., et al.

Serial No.: 09/758,993

Filed: January 12, 2001

For: **TETRAPARTATE PRODRUGS**

APPENDIX-Version with markings to show changes made

IN THE SPECIFICATION:

The paragraph beginning at page 2, line 20 has been amended as follows:

One way in which these problems have been addressed is described, for example, by co-owned patent applications Serial Nos. 09/183,557, filed October 30, 1998, now U.S. Patent No. 6,180,095 and 08/992,435, filed on December 17, 1997, now abandoned. These teach double prodrugs, i.e., tripartate, that comprise polymer conjugates of various biologically-effective materials, and methods of making these conjugates. The double prodrug linkages are selected to hydrolyze *in vivo* at a rate which generates sufficient amounts of the "second" and more reactive prodrug compound within a suitable time after administration by, e.g., a 1,4-aryl or 1,6-aryl (e.g., benzyl) elimination reaction, providing improved control of the pharmacokinetics of a number of small molecule drugs, agents and the like. However, further opportunities for particularly selective targeting of diagnostic and/or therapeutic agents to tissues or cells of interest, by means of a rationally designed prodrug conjugate remain.

The paragraph beginning at page 5, line 2 has been amended as follows:

When Z includes at least one amino acid residue, the amino acid is, e.g., alanine, valine, leucine, isoleucine, glycine, serine, threonine, methionine, cysteine, phenylalanine, tyrosine, tryptophan, aspartic acid, glutamic acid, lysine, arginine, histidine, proline, and/or a combination thereof, to name but a few. When Z includes a peptide, the peptide ranges in size, for instance,

from about 2 to about 10 amino acid residues. In one preferred embodiment, the peptide is Gly-Phe-Leu-Gly (SEQ ID NO: 1) or Gly-Phe-Leu.

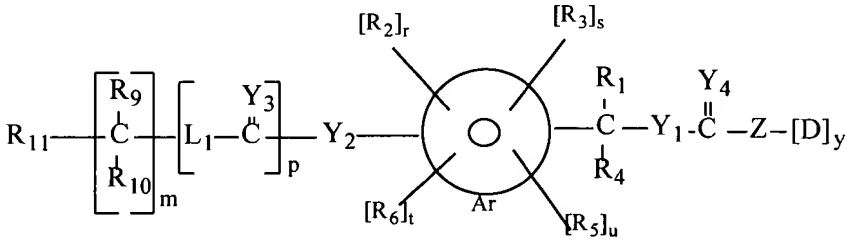
The paragraph beginning at page 20, line 8 has been amended as follows:

Suitable amino acid residues can be selected from naturally-occurring or synthetic, i.e. non-naturally-occurring, amino acids including alanine, valine, leucine, isoleucine, glycine, serine, threonine, methionine, cysteine, phenylalanine, tyrosine, tryptophan, aspartic acid, glutamic acid, lysine, arginine, histidine or proline. Some preferred peptide residues include Gly-Phe-Leu-Gly (SEQ ID NO: 1) and Gly-Phe-Leu. It is noted that the terminal amino group of the amino acid or peptide residue will be proximal to R_{11} (i.e. polymer). Peptides can be readily synthesized or obtained from commercial sources for inclusion herein.

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (Amended) A compound of Formula I:

(I) 

wherein:

L_1 is a bifunctional linking moiety;

D is a moiety that is a leaving group, or a residue of a compound to be delivered into a cell;

Z is covalently linked to $[D]_y$, wherein Z is selected from the group consisting of: a moiety that is actively transported into a target cell, a hydrophobic moiety, and combinations thereof;

Y_1, Y_2, Y_3 and Y_4 are each independently O, S, or NR_{12};

R_{11} is a mono- or divalent polymer residue;

R_1, R_4, R_9, R_{10} and R_{12} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, and substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, [and] cyano-, carboxy-, C_{1-6} carboxyalkyls and C_{1-6} alkylcarbonyls;

Ar is a moiety which when included in Formula (I) forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

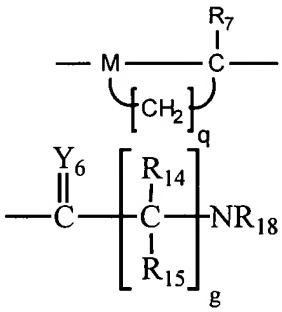
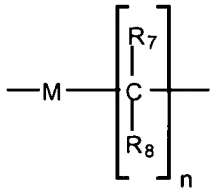
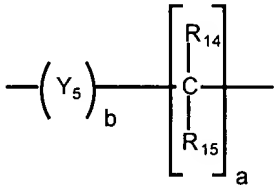
(m), (r), (s), (t), and (u) are independently zero or one;

(p) is zero or a positive integer; and (y) is 1 or 2;

wherein $Z[D]_y$ is capable of crossing the membrane of the and is capable of being hydrolyzed therein to release D.

Claim 2 has been amended as follows:

2. (Amended) The compound of claim 1, wherein L_1 is selected from the group consisting of:




and

;

wherein:

M is X or Q; where X is an electron withdrawing group;

Q is a moiety containing a free electron pair positioned three to six atoms from $-\overset{Y_3}{\overset{\|}{C}}-$;

(a) and (n) are independently zero or a positive integer;

(b) is zero or one;

(g) is a positive integer;

(q) is three or four;

R_7, R_8, R_{14}, R_{15} and R_{18} are independently selected from the group which defines R_9; and Y_5 and Y_6 are independently O, S, or NR_{12}.

Claim 6 has been amended as follows:

6. (Amended) The compound of claim 4 wherein the peptide ranges in size from [about] 2 to about 10 amino acid residues.

Claim 7 has been amended as follows:

7. (Amended) The compound of claim 6 wherein the peptide is Gly-Phe-Leu-Gly or (SEQ ID NO:1) Gly-Phe-Leu.

Claim 8 has been amended as follows:

8. (Amended) The compound of claim 1 wherein each D moiety is independently a residue of an active biological material [, or H].

Claim 9 has been amended as follows:

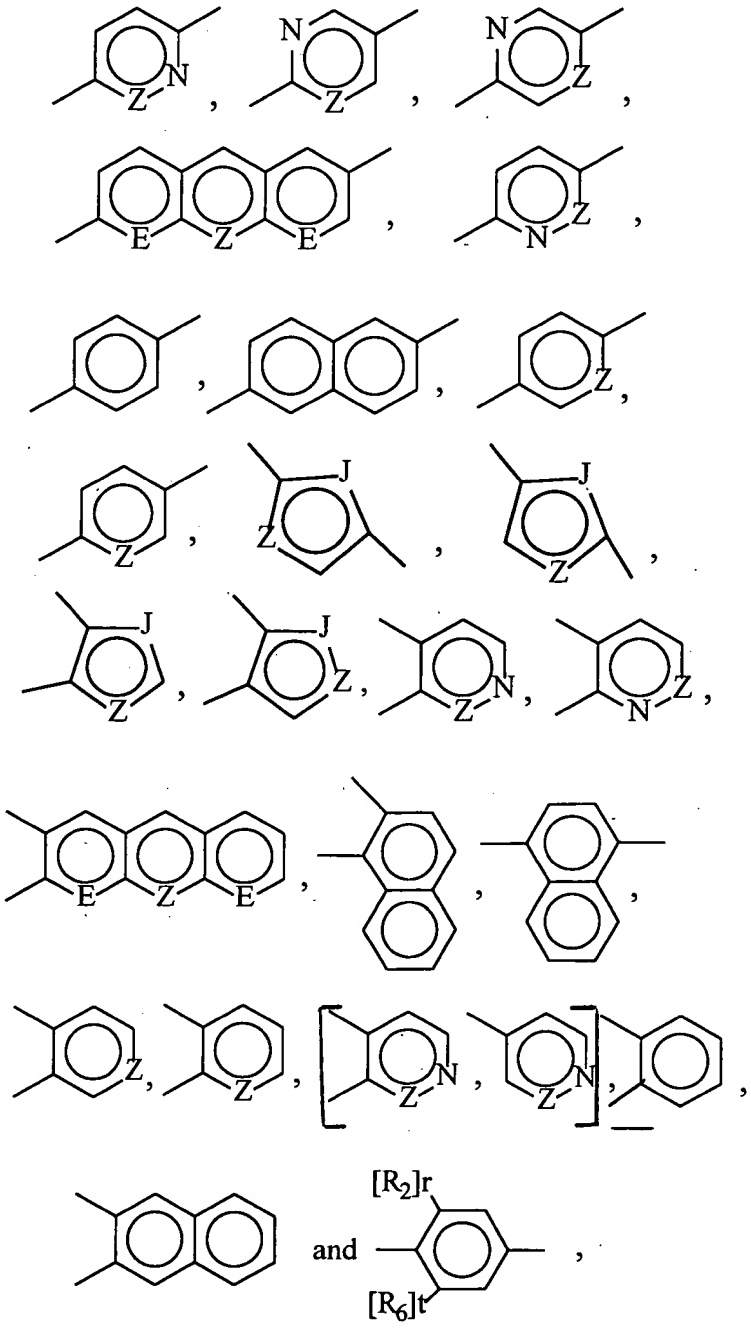
9. (Amended) The compound of claim 1 wherein each D moiety is independently a residue of an anticancer agent, an anticancer prodrug, a detectable tag, [and] or combinations thereof.

Claim 12 has been amended as follows:

12. (Amended) The compound of claim 1 wherein at least one D moiety is a leaving group selected from the group consisting of [as] N-hydroxybenzotriazolyl, halogen, N-hydroxyphthal-imidyl, p-nitrophenoxy, imidazolyl, N-hydroxysuccinimidyl, thiazolidinyl thione, and combinations thereof.

Claim 13 has been amended as follows:

13. (Amended) The compound of claim 1 wherein Ar is selected from the group consisting of,



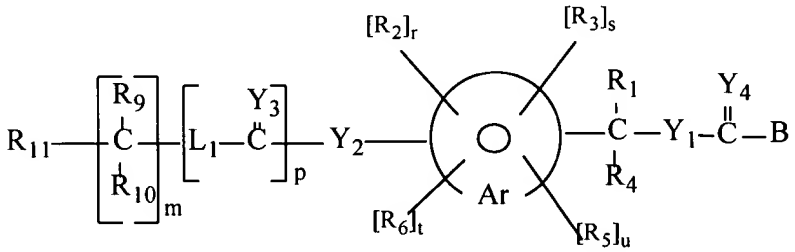
wherein J is selected from the group consisting of O, S, and N-R_{19}, E and Z are independently CR_{19} or N-R_{19} and R_{19} is selected from the group consisting of hydrogen, C_{1-6} alkyl,

C_{3-12} branched alkyl, C_{3-8} cycloalkyl, C_{1-6} substituted alkyl, C_{3-8} substituted cycloalkyl, aryls, substituted aryl, aralkyl, C_{1-6} heteroalkyl, and substituted C_{1-6} heteroalkyls.

Claim 17 has been cancelled.

Claim 31 has been amended as follows:

31. (Amended) A method of preparing a tetrapartate prodrug comprising reacting a compound of formula:

III 

with a compound of formula:

IV $\quad Lx - Z - [D]_y;$

wherein B is a leaving group for Formula III;

L_1 is a bifunctional linking moiety;

D is a moiety that is a leaving group, or a residue of a compound to be delivered into a cell;

Lx is a leaving group for Formula IV;

Z is covalently linked to $[D]_y$, wherein Z is selected from the group consisting of: a moiety that is actively transported into a target cell, a hydrophobic moiety, and combinations thereof;

R_1, R_4, R_9, R_{10} and R_{12} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, and substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, [and] cyano-, carboxy-, C_{1-6} [carboxyalkyl] carboxyalkyls and C_{1-6} [alkylcarbonyl] alkylcarbonyls;

Ar is a moiety which when included in Formula (III) forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

(m), (r), (s), (t), and (u) are independently zero or one;

(p) is zero or a positive integer;

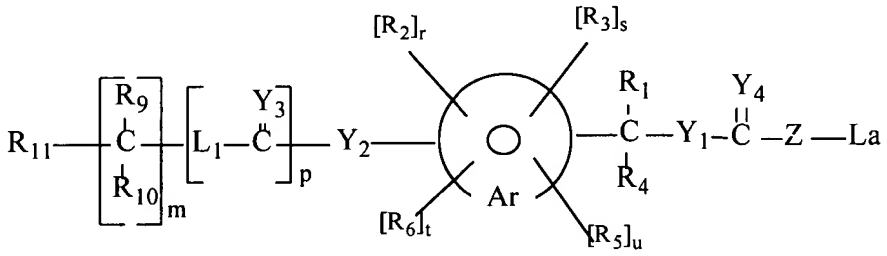
(y) is one or two; [and]

Y_1, Y_2, Y_3 and Y_4 are each independently O, S, or NR_{12} ; and

R_{11} is a monovalent or divalent polymer residue.

Claim 32 has been amended as follows:

32. (Amended) A method of preparing a tetrapartate prodrug comprising reacting a compound of formula

V 

with at least one biologically active material; wherein

L_1 is a bifunctional linking moiety;

La is a leaving group for Formula V;

Z is covalently linked to [at least one biologically active material,] La and wherein Z is selected from the group consisting of: a moiety that is actively transported into a target cell, a hydrophobic moiety, and combinations thereof;

R_1, R_4, R_9, R_{10} and R_{12} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, and substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, [and] cyano-, carboxy-, C_{1-6} [carboxyalkyl] carboxylalkyls and C_{1-6} [alkylcarbonyl] alkylcarbonyls;

Ar is a moiety which when included in Formula (V) forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

(m), (r), (s), (t), and (u) are independently zero or one;

(p) is zero or a positive integer;

Y_1, Y_2, Y_3 and Y_4 are independently O, S, or NR_{12} ; and

R_{11} is a monovalent or divalent polymer residue

wherein after the reaction Z is covalently linked to the at least one biologically active material.

Claim 33 has been amended as follows:

33. (Amended) A method of treating a disease or disorder in an animal, that comprises administering a pharmaceutically acceptable composition comprising an effective amount of a compound of claim 1,where D is a moiety that is a [leaving group, or a] residue of a compound to be delivered into a cell; to an animal in need thereof.